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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/677,983	FELDER ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9-21,25,26 and 28-46* is/are pending in the application.

4a) Of the above claim(s) *1-3,14-21,25,26,28-40 and 42-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-13,41,45 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/3/05 & 1/8/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendment to the specification, filed January 3, 2005, has been entered.

The Sequence Listing filed January 3, 2005 has been entered.

The preliminary amendment to the specification filed January 8, 2007 has been entered. However, the preliminary amendment to the claims, filed January 8, 2007, was not entered for reasons of record.

The preliminary amendment to the claims, filed April 2, 2007, has been entered. Claims 4-8, 22-24, and 27 have been cancelled and Claims 39-46 have been newly added.

Claims 1-3, 9-21, 25, 26, and 28-46 are pending in the instant application.

Applicants' election, with traverse, of Group III, Claims 9-13 and 22-24, in the response filed January 8, 2007 is acknowledged. The elected invention is drawn to a reconstituted system for assaying GRK4 activity, and a method of identifying putative anti-hypertensive agents by detecting GRK4 activity. On January 7, 2008, Applicants further elected species C, drawn to a GRK4 containing A486V, as set forth in the restriction requirement of July 3, 2007. The traversal is on the grounds that Group IV (Claims 14, 25, and 26) should be examined with Group III because the claims of Group IV also recite GRK4 protein. Applicants conclude that it would appear that the search that would be conducted to determine whether the claims of Group III are patentable, would be fairly, if not substantially coextensive with the search in connection with Group IV. This is not found persuasive because the restriction requirement of July 5, 2006 established that serious burden exists for the simultaneous examination of more than one invention group. First, with regard to burden, MPEP § 808.02 states that, to establish that there would be a serious burden on the examiner if restriction is not required,

> "the examiner must show by appropriate explanation one of the following:
> (A) **Separate classification thereof:** This shows that each invention has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search. Patents need not be cited to show separate classification." (emphasis original)

Thus, to establish that a serious burden exists, it is sufficient to show separate classification of the inventions. The instant inventions have separate classifications and require separate search. Accordingly, the searches for Groups III and IV are not coextensive. Second, the examination of Group III raises different non-prior art issues from the examination of Group IV. Burden pertains to both search and examination and, in the present case, there is both a search burden and examination burden when Groups III and IV are searched and examined together. See MPEP § 803.

Accordingly, the requirement is still deemed proper and is therefore made FINAL.

Claims 1-3, 14-21, 25, 26, 28-48, and 42-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on January 8, 2007.

Accordingly, Claims 9-13, 41, 45, and 46 are examined herein.

Drawings

Figures 1-5 are objected to because the meaning of the symbols "a", "#", "*" and "S" are not provided. Accordingly, the figure should not contain symbols that are not described. Figure 5 is further objected to because it is unclear how the filled (black) symbols differ from the open (white) symbols. According to the specification, the experiment was carried out using transfected Chinese hamster ovary (CHO) cells and there is nothing that explains why the data represented by the filled symbols differs from the data represented by the open symbols. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be

removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following issues:

As a first issure, there is a discrepancy in the description of the experiment depicted in Figure 5. The legend to Figure 5 at page 7, paragraph 0022 conflicts with the description of the experiment at page 37, paragraph 0073. The legend to Figure 5 says that the graph depicts experiments carried out using CHO cells that overexpress GRK4 gamma, whereas the description of the experiment at page 37, paragraph 0073 says that the CHO cells were transfected with wild-type or variant GRK4α cDNA. Paragraph 0073 consistently refers to GRK4α as the isoform being studied in that particular experiment.

As a second issue, there is a discrepancy in the description of the experiment depicted in Figure 4. The legend to Figure 4 at page 7, paragraph 0021 conflicts with the description of the experiment at page 37, lines 6-9. The legend to Figure 4 says that the graph depicts an experiment that shows an increase in GRK4 gamma/δ expression in renal proximal tubules in response to D1-like agonist stimulation in hypertensive but not in normotensive subjects, whereas the description of the experiment at page 37 says that the experiment showed that the D1-like agonist-mediated increase in GRK activity was associated with an increase in membranous expression of GRK4 α/δ in renal proximal tubule cells from hypertensive but not from normotensive subjects.

Appropriate correction is required.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120 is acknowledged. However, the provisional applications and parent applications upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for Claims 9-13, 41, 45, and 46 of this application, for the same reasons discussed hereinbelow as applied to the present application. Application serial nos. 60/071,199, 60/098,279, and parent application nos. PCT/US99/00663 and 09/674,748 fail to provide an **enabling disclosure** for the invention now being claimed in Claims 9-13, 41, 45, and 46, for the reasons discussed herein below as a rejection under 35 U.S.C. 112, first paragraph, as applied to the instant application. Likewise, the earlier-filed applications upon which priority is claimed fail to provide adequate **support** under 35 U.S.C. 112 for one or more claims of this application, for the same reasons discussed hereinbelow as a rejection under 35 U.S.C. 112, first paragraph, as applied to the present application.

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Thus, the earlier-filed applications do not meet the requirements under 35 U.S.C. 119(e) and 120 for the benefit of obtaining priority to an earlier-filed application.

Thus, the effective filing date for Claims 9-13, 41, 45, and 46 is October 2, 2003, the filing date of the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9-11, 13, 41, 45, and 46 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims encompass human beings, which are non-statutory subject matter. The specification discloses that both GRK4 and GRK4 substrates are expressed in humans. In particular, the specification discloses 4 isoforms of the human GRK4 protein, as well as a human dopamine D1 receptor. As such, the specification makes it clear that both GRK4 and a GRK4 substrate are present in humans.

Accordingly, the claimed reconstituted system encompasses non-statutory subject matter.

Claims 9-11, 13, 41, and 46 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims encompass products of nature, which are non-statutory subject matter.

The claims are drawn to a reconstituted system comprising GRK4 and a GRK4 substrate. The specification refers to various systems that may comprise GRK4 and a GRK4 substrate, including whole cells and animals (page 6, paragraph 0015 and paragraph 0039 at pages 24-25). The specification specifically states that "[i]n general, any system that contains GRK4 and a GRK4 substrate, and from which GRK4 conformation or activity (and changes therein) can be measured, may be used in order to screen substances for anti-hypertensive activity" (page 25, lines 1-3). Accordingly, the claims encompass products of nature, which are non-statutory subject matter. Both GRK4 and GRK4 substrates are expressed in rats and humans. As such, the claims cover animals, particularly rats and humans, as well as renal proximal tubule cells residing *in vivo* in an animal, which are products of nature and therefore non-statutory subject matter. See also the art rejection set forth below.

Accordingly, the claimed reconstituted system encompasses non-statutory subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 10-12 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite a functional fragment of a D1 receptor. However, the specification does not provide a written description of functional fragments of a D1 receptor or functional fragments. The specification does not clearly define the intended scope of the phrase "functional fragment" and it is unclear what particular function is being referred to. In the absence of a clear definition, the phrase encompasses a wide variety of fragments and there is no requirement that any essential part of the reference molecule remain as part of the "functional fragment." In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, only a single embodiment, i.e. the full-length D1 receptor, is described by its complete structure. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, the specification does not describe functional fragments by other relevant identifying characteristics. Furthermore, there is no requirement that any essential part of the reference protein remain as part of the "functional fragment." This limited information is not deemed sufficient to

reasonably convey to one skilled in the art that Applicants were in possession of functional fragments as recited in the claims, at the time the application was filed. Thus, it is concluded that the written description requirement is not met for the claimed genus of functional fragments.

Claim 9-13, 41, 45, and 46 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

Giving due consideration to all the *Wands* factors, with the most relevant factors discussed hereinbelow, it is concluded that the specification fails to provide an enabling disclosure for the full scope of the claims, for the reasons that follow.

Nature of the invention and breadth of the claims. The claims are drawn to a reconstituted system that measures GRK activity, comprising GRK4 and a GRK4 substrate. Claim 10 is directed to the reconstituted system comprising GRK4 and a GRK 4 substrate, wherein the GRK4 substrate is a D1 receptor or a functional fragment thereof. Claim 11 is directed to the reconstituted system of Claim 10, which is a whole cell that expresses GRK4 and said GRK4 substrate. Claim 12 is directed to the reconstituted system of Claim 11, wherein said whole cell is a Chinese hamster ovary cell transfected with a first heterologous gene encoding a D1 receptor and a second heterologous gene encoding a GRK4

protein associated with hypertension. Claim 13 is directed to the reconstituted system of Claim 9, wherein said GRK4 protein is associated with essential hypertension. Claim 41 is directed to the reconstituted system of Claim 9, wherein the GRK4 is a GRK4 containing A486V. Claim 45 is directed to the reconstituted system of Claim 9, which comprises a lipid micelle. Claim 46 is directed to the reconstituted system of Claim 11, wherein the whole cell comprises a HEK, LTK, MDCK or LLCPK cell. The claims cover compositions containing any GRK4 protein from any animal species and covers a wild-type GRK4 protein as well as any mutant form or polymorphic form of the protein. The claims also cover compositions containing any isoform of the GRK4 protein from any animal species, including any mutant form of any isoform, in addition to the wild-type isoform. The claims also cover any cell type comprising any GRK4 protein in combination with any GRK4 substrate. Accordingly, the claims cover a wide variety of different compositions.

Amount of direction or guidance presented and presence or absence of working examples. The specification teaches that fenoldopam stimulation of renal proximal tubule cells from hypertensive subjects showed lower levels of cAMP accumulation than did cells from normotensive subjects, thereby demonstrating an uncoupling defect in hypertensive subjects (see Figure 2). To determine whether an increase in GRK4 activity was responsible for the uncoupling of the D1 receptor in renal proximal tubule cells in hypertension, the effect of D1-like agonist stimulation on cAMP accumulation after inhibition of GRK4 translation by antisense was studied (page 33, paragraph 0064). The study showed that GRK4 antisense enhanced the ability of fenoldopam, a D1-like agonist, to stimulate cAMP accumulation in cells from hypertensive subjects (page 33, paragraph 0064, last sentence and Figure 2). The specification concludes that the uncoupling of the D1 receptor is due to increased GRK4 activity in hypertension.

The specification further teaches some polymorphisms within the GRK4 protein that are associated with hypertension and others that are not (pages 34-36). In particular, the R65L, A142V, and

A486V polymorphisms, which result from single nucleotide polymorphisms, appear to be associated with hypertension. The V247I and D562G polymorphisms do not appear to be associated with hypertension.

The specification alleges that certain polymorphic forms of **GRK4α** are associated with hypertension (see page 37, paragraph 0073, lines 6-9). In particular, the specification notes that the expression of wild type **GRK4α** decreased the ability of the D1 agonist to stimulate cAMP production and that the inhibition of the D1 agonist action became even greater with the **GRK4α** variants R65L and/or A486V. Thus, certain variations in the **GRK4α** gene are activating mutations. The specification does not disclose any polymorphic forms of any of the other GRK4 isoforms that are associated with essential hypertension in humans. Accordingly, the specification does not teach how to use an *in vitro* composition comprising a GRK4 isoform other than GRK4α. However, the teachings of the specification with regard to the activity of GRK4α are inconsistent. For example, with regard to the experiment depicted in Figure 1, the specification states that "it was concluded that GRK4α is not involved in the desensitization of the D_1 receptor" (page 37, lines 2-3). The specification further suggests that perhaps a GRK4 isoform that does not normally phosphorylate rhodopsin (only GRK4α phosphorylates rhodopsin) may have become activated in hypertension (page 37, paragraph 0071). However, the next sentence suggests that **GRK4δ** was responsible for the increased GRK activity (page 37, lines 6-9). Furthermore, the art teaches that it is the **GRK4γ** isoform and specific polymorphs of the **GRK4γ** isoform that are associated with essential hypertension in humans (Felder et al., 2002). Accordingly, the state of the art was such that it directly conflicted with the teachings of the instant specification in showing that activating mutations of **GRK4γ** are associated with essential hypertension in humans. In view of the conflicting assertions of the instant specification with regard to the relevant functions of the different isoforms, no scope of enablement has been indicated.

As noted above, the claims cover any cell type comprising any GRK4 protein in combination with any GRK4 substrate. While the specification discloses that renal proximal tubule cells and testis

cells endogenously express GRK4 proteins and D1 receptors, the specification does not disclose any other cell type that naturally expresses a GRK4 protein and GRK4 substrate. Therefore, the specification does not enable a cell type that provides endogenous expression of these components other than the renal proximal tubule cell and testis cell described in the instant specification. While the specification provides guidance for transfecting various cell types with a GRK4 cDNA and cognate receptor cDNA, the guidance for non-transfected cell types that naturally express a GRK4 and GRK4 substrate is limited to the proximal tubule cells and testis cells.

State of the prior art and level of predictability in the art. The specification teaches that a reconstituted system comprising a GRK4 protein and a GRK4 substrate can be used as an assay system for the identification of antihypertensive agents. The claims cover systems that comprise a wide variety of mutant forms of the GRK4 protein, including mutant forms of any of the 6 disclosed isoforms. However, the state of the art was such that the function of mutant proteins could not be predicted from the primary structure of the protein. Absent information on how the mutation affects the function of the protein, the skilled artisan would not know how to use the wide variety of mutant proteins covered by the claims. Accordingly, the skilled artisan would not know how to use the claimed reconstituted systems over the full scope, which includes all mutant and polymorphic forms of GRK4 from any animal species.

The specification fails to provide an enabling disclosure for the claimed compositions, where any polymorphism or mutation within the GRK4 protein is considered to be correlated with essential hypertension, because neutral mutations and inactivating mutations are also known in the art and GRK4 proteins containing these type of mutations would not be useful for identifying antihypertensive agents. Such polymorphs (or mutant forms) would not result in desensitization of the D1 dopamine receptor. Elseth et al. (1995, Principles of Modern Genetics) teaches that, since amino acids with similar structures are more often than not coded for by similar codons, missense mutations often involve amino acids with similar chemical properties. When the substituted amino acid can participate in the appropriate interchain

bonding, the normal folding pattern and protein function will be maintained (p. 545). At page 545, Elseth et al. further states that

> It is thus quite possible that an alteration in the amino acid sequence will not manifest itself by altering the activity of the protein. A missense mutation that does not change the function of the protein is sometimes referred to as a neutral mutation.

The instant specification teaches that mutant forms of **GRK4α** that inhibit transduction of a dopaminergic signal correlate with a predisposition to essential hypertension (see page 38, lines 2-5). In particular, the specification concludes that "[t]he functional studies in renal proximal tubule cells and the expression studies in CHO cells suggest that an increased activity of **GRK4α** is responsible for the decreased ability of D1 receptor ligands to couple to effector enzymes and ion transport proteins in hypertension" (page 38, lines 2-5, emphasis added). Thus, the skilled artisan would not know how to use compositions containing mutant forms of GRK4 that do not exhibit increased activity, because the specification teaches that the claimed compositions are useful for identifying antihypertensive agents, but the specification clearly teaches that only GRK4 mutants comprising activating mutations would be useful in assays for identifying antihypertensive agents. The specification does not teach how to use compositions containing mutant forms of GRK4 that do not exhibit increased activity. Accordingly, the skilled artisan would not know how to use compositions containing mutant forms of GRK4 that do not exhibit increased activity.

The specification fails to provide an enabling disclosure for the full scope of the claimed compositions because, at the time of the invention, the state of the art was such that the effect of amino acid mutations on protein activity was unpredictable.

The state of the prior art is such that the skilled artisan cannot predict the effect of mutations within a polypeptide chain and therefore cannot predict which mutations will confer a desired biological activity to a protein of interest. It is well known in the art that a single amino acid mutation can result in altered protein function, but without predictability of which mutations will lead to what types of alteration in function. **Pakula et al.** (1989, Annu. Rev. Genet. 23: 289-310) teaches that at sites of key

determinants of protein stability or activity, even a single conservative substitution can have severe phenotypic effect. Further, Pakula et al. teaches that conservative amino acid substitutions and proteins with 80% or 95% homology do not necessarily possess the same function/activity of the parent protein. Unfortunately, this means that there is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone. As a specific example, **Ju et al.** (1991, PNAS 88: 2658-2662) teaches that a single amino acid substitution produces an analog of an IL-1 receptor antagonist that exhibits agonist activity. A single amino acid substitution produces a protein with a direct opposite effect, as compared to the original protein. This teaching further emphasizes that it is not possible to ascribe a biological activity to a protein based on homology considerations alone, because a single amino acid substitution can have a profound effect on the activity of a protein. **Witkowski et al.** (1999, Biochemistry 38: 11643-11650) teach that a single amino acid substitution results in conversion of a parent polypeptide's activity from a beta-ketoacyl synthase to a malonyl decarboxylase (Table 1, p. 11647). Thus, the state of the art shows that the effect of various mutations on the activity of a polypeptide is highly unpredictable.

The activity of a protein cannot be predicted from its structure alone or its homology to other proteins. These observations are further supported by the studies of **Skolnick et al.** (2000, Trends in Biotech. 18: 34-39) teaches that "..sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (abstract). Skolnick further notes that "knowing a protein's structure does not necessarily tell you its function" and "[b]ecause proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (page 36, column 1, box 2). The reference shows that even a core amino acid sequence can show diverse biological functions when

surrounded by different background amino acid sequences. Therefore, the art acknowledges that the activity of a protein was unpredictable from amino acid sequence at the time of the invention and that mutations resulting in a desired activity were likewise unpredictable.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970).

Relative level of skill of those in the art and quantity of experimentation necessary. Although the level of skill in the art is high, given the high degree of unpredictability in the protein art, the skilled artisan would be required to engage in intensive investigation, rather than routine experimentation to identify mutant or polymorphic forms of GRK4, other than those described in the instant specification, and correlate the genetic variants with functional consequences and disease associations. In view of the quantity of experimentation necessary to identify other GRK4 polymorphs, if any, the unpredictability of phenotypic consequences and the further unpredictability of finding other GRK4 polymorphs associated with essential hypertension in humans, and given the limited applicable working examples demonstrating a useful GRK4 polymorphs associated with human essential hypertension, the limited guidance in the specification with regard to the potential uses of the claimed reconstituted system, the broad scope of the claims with regard to the various GRK4 polymorphs covered along with the varied GRK4 substrates covered (i.e., any mutant or wild-type form of GRK4 from any species), and the unpredictability for using the claimed compositions as set forth in the specification,

undue experimentation would have been required for one skilled in the art to make and use the claimed compositions.

Given the limited guidance in the specification, the broad scope of the claims with regard to the multitude and types of mutations allowed, the unpredictability in the art, particularly the unpredictability for the effect of any given mutation or multitude of mutations as covered by the claims on the biological activity of a mutant polypeptide, and the limited working examples, one of skill in the art would have been required to engage in undue experimentation to make and use the claimed compositions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-13, 41, 45, and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-13, 41, 45, and 46 are indefinite in their recitation of the term "system" because the specification fails to define the term. Thus, the metes and bounds of the claimed system are not clearly set forth. For example, it is unclear if the term should be construed to include a freezer comprising a test tube comprising the requisite components of a GRK4 protein and GRK4 substrate.

Claim 9 is indefinite in its recitation of "a reconstituted system that measures GRK activity" because the claimed system does not measure GRK activity. The minimal system contains only a GRK4 protein and a GRK4 substrate which does not result in measurement of any activity. The preamble requires, however, a system that measures GRK activity. Claims 10-13, 41, 45, and 46 are indefinite insofar as they depend from Claim 9.

Claim 9 is indefinite in its recitation of "a reconstituted system that measures GRK activity, comprising GRK4 and a GRK4 substrate" because it is unclear how a GRK4 protein could be used to

measure the activity of other GRK proteins such as GRK1 (rhodopsin kinase) or GRK2 (β-adrenergic receptor kinase 1). A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, Claim 9 recites the broad recitation GRK, and the claim also recites GRK4 which is the narrower statement of the range/limitation. Claims 10-13, 41, 45, and 46 are indefinite insofar as they depend from Claim 9.

Claim 46 is indefinite in its recitation of "wherein the whole cell comprises a HEK, LTK, MDCK or LLCPK cell" because it is unclear how a cell can comprise a cell. Tissues can comprise cells and cells can comprise subcellular components, but a cell cannot comprise a cell.

Claim 46 is indefinite in its recitation of "a HEK, LTK, MDCK or LLCPK cell" because abbreviations should be accompanied by the complete term where they first appear in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Sallese et al. (1997, J. Biol. Chem. 272(15): 10188-10195).

Sallese et al. (1997) disclose an *in vitro* assay for measuring the activity of GRK4. Partially purified GRK4 was incubated with rhodopsin in the presence of light (page 10189, column 1, paragraph 3). Figure 1 shows that partially purified GRK4α did phosphorylate rhodopsin, while the other three isoforms, GRK4β, GRK4γ, and GRK4δ, did not phosphorylate rhodopsin. Accordingly, rhodopsin is a GRK4 substrate, as set forth in the present claims. The assay system disclosed thus includes a GRK4 protein and a GRK4 substrate, as set forth in the present claims. Furthermore, the assay system can be used to measure GRK4 activity, as detection of radioactively-labeled substrate on a polyacrylamide gel demonstrates substrate phosphorylation.

With regard to Claim 13, which recites the limitation "wherein said GRK4 protein is associated with essential hypertension," the reference discloses an assay system comprising GRK4γ and rhodopsin (see Figure 1c). GRK4γ is a GRK4 protein associated with hypertension, as this is an inherent property of the protein. Furthermore, although GRK4γ does not phosphorylate rhodopsin, rhodopsin is nevertheless a GRK4 substrate for the reasons discussed above.

The MPEP states that the "express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103." MPEP § 2112. Also see the decision of *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) which states that "[t]he inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." The MPEP further emphasizes that the "inherent feature need not be recognized at the time of the invention" (MPEP § 2112).

MPEP § 2112 explicitly states the following:

> "SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY
> 'The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.' *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

The MPEP further teaches that "once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to the applicant to show an unobvious difference." MPEP § 2112.

In the decision of *In re Spada*, 15 USPQ2d 1655 (CAFC 1990) the court points out that discovery of a new property or use of a previously known composition, even if unobvious from prior art, cannot impart patentability to claims to known compositions. A reconstituted system comprising GRK4 and a GRK4 substrate, wherein said GRK4 protein is associated with essential hypertension constitutes "a previously known composition."

Thus, the claimed invention is disclosed in the prior art.

Claims 9, 13, and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Premont et al. (1996, J. Biol. Chem. 271(11): 6403-6410).

Premont et al. (1996) disclose the coexpression of GRK4 and rat luteinizing hormone/chorionic gonadotropin (LH/CG) receptor in HEK293 cells (abstract and page 6404, column 2, paragraph 5). The reference further discloses *in vitro* receptor phosphorylation assays where partially purified GRK4 was incubated with β_2-adrenergic receptor in vesicles (page 6404, column 2, last paragraph and Figure 7). Human β_2-adrenergic receptors were purified and reconstituted in phospholipid vesicles. Receptors were reconstituted in vesicles of 100% phosphatidylcholine or in vesicles of 5% phosphatidylinositol 4,5-bisphosphate (PIP_2) and 95% phosphatidylcholine. Figure 7 shows that GRK4α does phosphorylate the β_2-adrenergic receptor. Accordingly, the β_2-adrenergic receptor is a GRK4 substrate, as set forth in the

present claims. The assay system disclosed thus includes a GRK4 protein and a GRK4 substrate, as set forth in the present claims. Furthermore, the assay system can be used to measure GRK4 activity, as detection of radioactively-labeled substrate on a polyacrylamide gel demonstrates substrate phosphorylation. The reference further discloses HEK293 cells transfected with LH/CG receptor cDNA and GRK4γ cDNA (Figure 6). Assays measuring the accumulation of cAMP were carried out (Figure 6).

With regard to Claim 13, which recites the limitation "wherein said GRK4 protein is associated with essential hypertension," the reference discloses an assay system comprising GRK4γ and the LH/CG receptor (see Figure 6). GRK4γ is a GRK4 protein associated with essential hypertension, as set forth in the claim, as this is an inherent property of the GRK4γ protein, insofar as certain polymorphic forms of GRK4γ exhibit increased activity and consequently hyperphosphorylate their cognate receptor.

The MPEP states that the "express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103." MPEP § 2112. Also see the decision of *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) which states that "[t]he inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." The MPEP further emphasizes that the "inherent feature need not be recognized at the time of the invention" (MPEP § 2112).

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> 'The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.' *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

The MPEP further teaches that "once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the examiner presents evidence or reasoning tending to show inherency, the burden shifts to the applicant to show an unobvious difference." MPEP § 2112.

In the decision of *In re Spada*, 15 USPQ2d 1655 (CAFC 1990) the court points out that discovery of a new property or use of a previously known composition, even if unobvious from prior art, cannot impart patentability to claims to known compositions. A reconstituted system comprising GRK4 and a GRK4 substrate, wherein said GRK4 protein is associated with essential hypertension constitutes "a previously known composition."

Thus, the claimed invention is disclosed in the prior art.

Claims 9-13, 41, 45, and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Felder et al. (3/19/2002, PNAS 99(6): 3872-3877).

Felder et al. (2002) disclose CHO cells stably transfected with D_1 receptor and GRK4γ cDNAs subcloned into a pTet-off vector (see Figure 4 and page 3873, paragraph bridging columns 1-2). The reference further discloses cultured human renal proximal tubule cells which comprise both GRK4 and the D1 receptor (page 3873, column 1, paragraphs 2-3).

Thus, the claimed invention is disclosed in the prior art.

Claims 9-11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamaguchi et al. (1993, Am. J. Physiol. Renal Physiol. 264: 280-285), as evidenced by Virlon et al. (1998, Endocrinology 139(6): 2784-2795; cited on IDS of 1/3/05).

The claims are directed to a reconstituted system that measures GRK activity, comprising GRK4 and a GRK4 substrate. The specification refers to various systems that may comprise GRK4 and a GRK4 substrate, including whole cells and animals (page 6, paragraph 0015 and paragraph 0039 at pages 24-25). The specification specifically states that "[i]n general, any system that contains GRK4 and a GRK4 substrate, and from which GRK4 conformation or activity (and changes therein) can be measured, may be

used in order to screen substances for anti-hypertensive activity" (page 25, lines 1-3). Accordingly, the claims read on rats, which are a product of nature, as noted above in the rejection under 35 U.S.C. 101.

Yamaguchi et al. disclose rats. The reference further discloses that rats comprise dopamine D1A receptors in various tissues. Rats also comprise GRK4 protein, as evidenced by Virlon et al. Accordingly, rats comprise both GRK4 and a GRK4 substrate.

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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